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THE ASYMPTOTIC DISTRIBUTION OF MORTALITY RATES IN COMPETING RIS--ETC(U)
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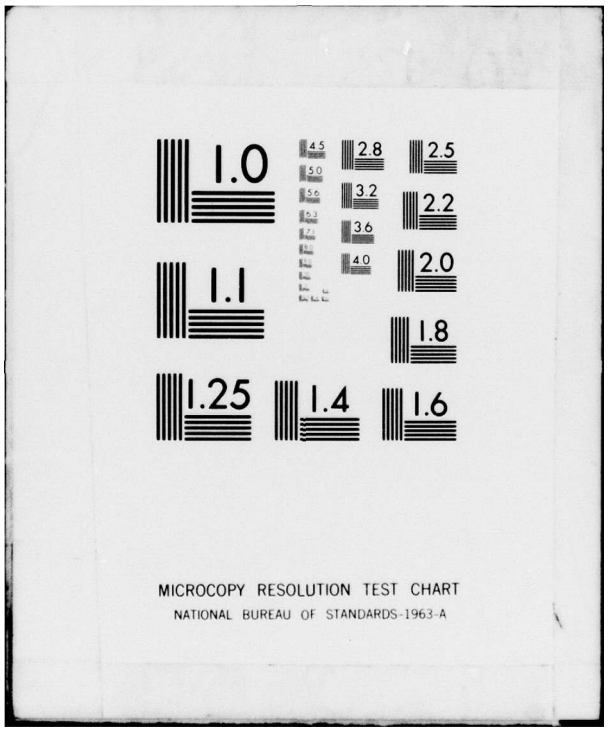
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(6) THE ASYMPTOTIC DISTRIBUTION OF MORTALITY RATES IN COMPETING RISKS ANALYSES,

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Summary

For a sample of individuals from an animal or human population under observation in a clinical trial or life test, mortality rates are defined for each risk to which the population is exposed. By considering only the crude risk functions and cause-specific failure rates in a basic competing risks model, these mortality rates are shown to have an asymptotic normal distribution. An expression for the asymptotic correlation between a pair of mortality rates is thus obtained and a necessary and sufficient condition for their asymptotic independence is investigated in some general situations with reference to only the cause-specific failure rates and the survival function of the individuals.

Key Words: Asymptotic independence, competing risks, mortality rates, multivariate normal distribution, survival analysis.

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1. Introduction

We shall consider here a basic statistical model in which an animal or human population is under insult by a totality of k mutually exclusive competing risks. We are concerned with experiments in which a subpopulation of n units is under continual surveillance from the onset with the time and type of occurrence of the responses monitored, whenever possible, for each unit. The term 'response' is given a wide interpretation and encompasses a broad class of response data from clinical and epidemiologic studies in which the nature of the observed response can be attributed to exactly one of several causes. In a variety of such investigations a group of individuals may be followed with interest in a specific cause of the observed response. For instance in a laboratory animal experiment concerned with the exposure to certain carcinogenic pollutants the terminal response may be the appearance of a tumor or death caused by one of several organotropic carcinomas -- intestine, bladder, lung, liver -- but concern may be focused on only one specific carcinoma. Experiments of this type are often complicated by the presence or need for censoring designs. Limitations on time or economic considerations may prevent the luxury of prolonged experimentation beyond specified constraints or, in some instances, a desire for a preliminary analysis of the current accumulated information in a study necessarily entails incomplete data. On the other hand withdrawals from a clinical study and subsequent loss to follow-up must be considered in some analyses.

In this paper we consider the mortality or response rate of the competing factors evaluated from data recorded in a clinical trial or life test in which n specimens are observed either throughout their lifetime or over a duration of time (Type I censoring). The statistical model which

we describe will also permit for designs in which items are withdrawn from observation at random (Random censoring).

The mortality rate for a risk type is defined as the ratio of the observed frequency of failures among the n specimens attributed to that risk to the total observation time for all units. However, as the occurrence of a failure by one cause necessarily precludes failure by the other risks these mortality rates will in general be dependent and thus any statistical procedures based on them for inferences on a particular risk type should take into account the extent of the possible influence of the remaining risks. We shall show that under very general conditions the vector of mortality rates for the k competing risks operating on a random sample of n specimens has a limiting k-variate normal distribution. An explicit expression for the asymptotic correlation of a pair of mortality rates is obtained and the sign of this correlation is seen to be related to the monotonicity of the cause-specific failure rates of the individual risks (when all risks are operative). Examples are cited where this correlation is zero thereby ensuring asymptotic independence of these two rates. We also explore this in the proportional hazards model of Chiang (1968).

The evaluation of mortality rates and their use in some survival analyses have been studied by several researchers in recent times. Tolley and Norman (1979), Vaeth (1979) and Zelen and Dannemiller (1961) draw attention to the possible influence of competing risks on a specific mortality rate under study. Our results based on very general assumptions (see Section 2) indicate, at least asymptotically, the extent of this dependency and now allow for procedures under broader conditions. Byar (1977) has advocated the use of mortality rates evaluated from various categories defined by prognostic variables in some medical statistical

investigations and has given testing procedures for the homogenity of these rates on the assumption that the response times of the competing variables follow exponential distributions. A more general picture now emerges from our results.

2. Preliminaries

We consider a random sample of n specimens under observation from the onset until time t. For each subject we record either the time of failure (death) Y and the associated cause, or the censoring time t. The variable $J \in \{1,\ldots,k\}$ labels the specific cause of failure, if observed before censoring. For the purpose of our analysis it is not necessary to consider latent (conceptual) life times corresponding to the various risks and a joint distribution of these lifetimes as is customary in some situations (for example, Moeschberger and David (1971), Hoel (1972), Gail (1975) and Elandt-Johnson (1976)). Tsiatis (1975) and Peterson (1976) have discussed the serious identifiability problems that rise in connection with assumptions about this joint distribution of conceptual life times when employing data of the type (Y,J). Accordingly we shall only deal with the absolutely continuous functions Q_i, called crude risks, defined by

$$Q_i(t) = P[Y \leq t, J = i], \; t \geq 0, \; i = 1,\ldots,k \tag{1}$$

and the cause-specific failure rates g_i given by

$$g_i(t) = \lim_{\Delta t \to 0} P[t < Y \leq t + \Delta t, J = i | Y > t]/\Delta t, \; i = 1,\ldots,k. \tag{2}$$

We may interpret $g_i(t)$ as the instantaneous probability of failure by cause i at time t when all risks are operative, given survival from all risks up to time t. In some contexts the g_i have also been referred

to as the rates of decrement, hazard rates, forces of mortality and intensity rates. Now, by virtue of (1) and (2) we have

$$Q_i(t) = \int_0^t g_i(y)S(y)dy, \quad t \geq 0 \tag{3}$$

where

$$S(t) = P[Y > t], \ t \geq 0 \tag{4}$$

is called the survival function of the units. Since the k risks are mutually exclusive and exhaustive one has

$$\sum_{i=1}^{k} Q_i(t) = 1 - S(t) \quad \text{and} \quad \sum_{i=1}^{k} Q_i(\infty) = 1 \ . \tag{5}$$

Throughout this paper we make the mild assumption that $EY > 0$ and. $EY^2 < \infty$.

Suppose the n subjects are monitored over the time interval $[0,t)$. The total observation time is

$$T_n(t) = \sum_{\ell=1}^{n} Y_\ell \wedge t \tag{6}$$

and the number of recorded failures due to cause i is

$$D_{n,i}(t) = \sum_{\ell=1}^{n} I[Y_\ell \leq t, J_\ell = i] \ . \tag{7}$$

Here $x \wedge y = \min(x,y)$ and $I(A)$ denotes the indicator of a set A. In some contexts $T_n(t)$ has been designated the 'time on trial' or 'person years at risk' of the sample. The mortality rate for the cause i evaluated from this information recorded in the interval $[0,t)$ is defined as

$$\Gamma_{n,i}(t) = D_{n,i}(t)/T_n(t). \tag{8}$$

We are interested in the vector of mortality rates designated by

$$\underset{\sim}{\Gamma}_n(t) = (\Gamma_{n,1}(t),\ldots,\Gamma_{n,k}(t)). \tag{9}$$

If all units are monitored over their entire life time the corresponding mortality rates can be obtained from the above by setting t equal to infinity. To deal with random withdrawals we suppose each individual has its own withdrawal time Z and so corresponding to (6) and (7) we may define

$$T_n^* = \sum_{\ell=1}^{n} Y_\ell \wedge Z_\ell;\ D_{n,i}^* = \sum_{\ell=1}^{n} I[Y_\ell \le Z_\ell,\ J_\ell = i],\ 1 \le i \le k\ . \qquad (10)$$

In this formulation we may consider withdrawals as a competing risk with its own survival time Z. With this interpretation the situation reduces to that of observing the sample until all units have responded.

3. Distribution of mortality rates and discussion

In view of our definitions (1) and (4) we obtain from (6) and (7), for each i, $1 \le i \le k$ and $t \ge 0$

$$E\, D_{n,i}(t) = \sum_{\ell=1}^{n} P[Y_\ell \le t,\ J_\ell = i] = n\, Q_i(t), \qquad (11)$$

$$E\, T_n(t) = \sum_{\ell=1}^{n} \int_0^t P[Y_\ell > y]dy = n \int_0^t S(y)dy. \qquad (12)$$

Therefore using (3) we define the vector $\underset{\sim}{\gamma}(t) = (\gamma_1(t),\ldots,\gamma_k(t))$ where

$$\gamma_i(t) = \frac{E\, D_{n,i}(t)}{E\, T_n(t)} = \frac{\int_0^t g_i(y)S(y)dy}{\int_0^t S(y)dy}\ ,\ 1 \le i \le k,\ t \ge 0\ . \qquad (13)$$

We shall also deal with a $k \times k$ matrix $\underset{\approx}{\Sigma}(t)$ whose (i,j)th element $\sigma_{ij}(t)$ is given by

$$\sigma_{ij}(t) = \{\int_0^t S(y)dy\}^{-2}\{Q_i(t)(\tfrac{1}{2}\,\delta_{ij} - C_j(t)) + Q_j(t)(\tfrac{1}{2}\,\delta_{ij} - C_i(t))\}, \qquad (14)$$

$1 \le i, j \le k$, where δ_{ij} is the Kronecker delta ($\delta_{ii} = 1$, all i and

$\delta_{ij} = 0$ otherwise) and $C_i(t)$ is defined by

$$C_i(t) = \left[\frac{\int_0^t y\, g_i(y)S(y)dy}{\int_0^t S(y)dy} - \frac{(\int_0^t g_i(y)S(y)dy)(\int_0^t yS(y)dy)}{(\int_0^t S(y)dy)^2} \right] . \qquad (15)$$

Proposition. With t held fixed and $\chi(t)$, $\Sigma(t)$ defined by (13) and (14) respectively

$$L[n^{\frac{1}{2}}(\underset{\sim}{\Gamma}_n(t) - \chi(t))] \to N_k(\underset{\sim}{0}, \Sigma(t)) \quad \text{as} \quad n \to \infty \ . \qquad (16)$$

Corollary. With the interpretation made on random withdrawals $L[n^{\frac{1}{2}}(\underset{\sim}{\Gamma}(\infty) - \chi(\infty))] \to N_k(\underset{\sim}{0}, \Sigma(\infty))$ as $n \to \infty$.

The proof of the proposition will be taken up in the next section. We devote the remainder of this section to some remarks and examples.

Remark 1. From (14) we have that the asymptotic correlation between the mortality rates $\Gamma_i(t)$ and $\Gamma_j(t)$ is

$$\frac{-(Q_i(t)C_j(t) + Q_j(t)C_i(t))}{\sqrt{Q_i(t)Q_j(t)(1 - 2C_i(t))(1 - 2C_j(t))}}$$

and thus (16) provides a necessary and sufficient condition for the asymptotic independence of these rates, namely

$$Q_i(t)C_j(t) + Q_j(t)C_i(t) = 0.$$

An analogous statement can be made in the case where experimentation is monitored throughout the life time of all units of the sample.

Remark 2. We shall show that the $C_i(t)$ of (15) may be interpreted as covariances. To see this let us define a nonnegative random variable W_t whose probability density function is $S(x)/(\int_0^t S(y)dy)$, for $x \in [0,t]$ and zero otherwise. Then (15) may be rewritten as $C_i(t) = \mathrm{Cov}(W_t, g_i(W_t))$. Hence with t held fixed, $C_i(t) \geq 0$ (respectively ≤ 0) according as the cause-specific failure rate $x \to g_i(x)$ is nondecreasing (respectively

nonincreasing) in $[0,t)$. In particular $C_i(t) = 0$ if $x \to g_i(x)$ is a constant function on $[0,t)$. Note that $C_i(t)$ is never zero if g_i is (strictly) increasing or decreasing over $[0,t)$. Similar remarks hold in the situation in which the sample is monitored until all units have failed.

Remark 3. Now if for a pair of risks i,j the failure rates g_i, g_j are both nondecreasing (respectively nonincreasing) in $[0,t)$, the asymptotic correlation of the mortality rates $\Gamma_i(t)$, $\Gamma_j(t)$ will be nonpositive (respectively nonnegative). In particular when both g_i, g_j are constant functions on $[0,t)$, this correlation is zero and hence from (16) this ensures the asymptotic independence of the rates $\Gamma_i(t)$ and $\Gamma_j(t)$. It may also be noted that if all g_i are constant over $[0,\infty)$, then the hazard rate corresponding to the survival time Y is also constant $(= \sum_{i=1}^{k} g_i)$, whence Y must have the exponential distribution.

We present an example in which the mortality rates are asymptotically independent even though the corresponding failure rates are nonconstant.

Example 1. Consider a life test in which n items are observed throughout their life time. We specify a competing risks model with crude risk functions given by

$$Q_i(t) = \lambda_i(1 - \exp(-\lambda_i t)),\ t \geq 0,\ i = 1,2,$$

with $\lambda_1 > \lambda_2 > 0$ and $\lambda_1 + \lambda_2 = 1$. Then from (3) and (5) we have

$$S(t) = \lambda_1 \exp(-\lambda_1 t) + \lambda_2 \exp(-\lambda_2 t),\ t \geq 0$$

$$g_i(t) = \exp(-\lambda_i t)/S(t),\ t \geq 0,\ i = 1,2.$$

From the Corollary it will follow that the mortality rates $\Gamma_1(\infty)$, $\Gamma_2(\infty)$ are asymptotically independent provided $(Q_1(\infty)C_2(\infty) + Q_2(\infty)C_1(\infty)) = 0$. From (15) we have in general

$$C_i(\infty) = \frac{E[YI[J = i]]}{EY} - \tfrac{1}{2} Q_i(\infty) \frac{EY^2}{(EY)^2}.$$

For our example a straightforward calculation shows

$$EY = \int_0^\infty S(y)dy = 2;$$

$$EY^2 = 2\int_0^\infty y\, S(y)dy = 2(\lambda_1^{-1} + \lambda_2^{-1}).$$

Also $Q_i(\infty) = \lambda_i$ and $E(YI(J = i)) = \int_0^\infty y\, Q_i'(y)dy = 1$; $i = 1,2$. Hence

$$C_1(\infty) = \tfrac{1}{4}(1 - \lambda_1\lambda_2^{-1}),$$

$$C_2(\infty) = \tfrac{1}{4}(1 - \lambda_2\lambda_1^{-1})$$

and therefore $(Q_1(\infty)C_2(\infty) + Q_2(\infty)C_1(\infty)) = 0$. We note that g_1 is strictly decreasing and g_2 strictly increasing whence in view of Remark 2, $C_1(\infty) < 0$ and $C_2(\infty) > 0$ as is the case.

Remark 4. From our assumptions the total failure (hazard) rate corresponding to the survival time Y is $h(t) = \sum_{i=1}^{k} g_i(t)$ with $h(t) = -S(t)/S'(t)$. Now suppose Chiang's proportionality assumption holds, namely $g_i(t) = c_i h(t)$, where the c_i (> 0) satisfy $\sum_{i=1}^{k} c_i = 1$. Therefore if Y has increasing failure rate (IFR) then h and so all g_i will be increasing and so $C_i(t) > 0$ for all i and t. Hence any pair of mortality rates will be negatively correlated. Likewise if Y has decreasing failure rate (DFR) all pairs of mortality rates will be positively correlated. This holds for any truncation time t.

Again from (15), we obtain after some simplification

$$C = \sum_{i=1}^{k} C_i(\infty) = (1 - \tfrac{1}{2}\frac{EY^2}{(EY)^2}) .$$

Under the proportionality assumption $C_i(\infty) = c_i C$, for all i. Thus if Y has increasing failure rate average (IFRA) then $C > 0$ and again each pair of mortality rates $\Gamma_i(\infty)$, $\Gamma_j(\infty)$ will be negatively correlated. Of course if Y has IFR it has necessarily IFRA. Similar statements can be made when Y has decreasing failure rate average (DFRA).

Example 2. Suppose the crude risks are specified by

$$Q_i(t) = \mu_i\{\beta^{\alpha}\Gamma(\alpha)\}^{-1}\int_0^t y^{\alpha-1}e^{-y/\beta}dy, \quad t \geq 0,\ i = 1,\ldots,k$$

where α,β, all $\mu_i > 0$ and without loss of generality we take $\sum_{i=1}^{k}\mu_i = 1$. Here Γ denotes the gamma function. The survival time Y has the gamma distribution with parameters α,β. We get

$$S(t) = \{\beta^{\alpha}\Gamma(\alpha)\}^{-1}\int_t^{\infty} y^{\alpha-1}e^{-y/\beta}dy$$

and

$$g_i(t) = \mu_i\int_0^{\infty}(1 + t^{-1}y)^{\alpha-1}e^{-y/\beta}dy = \mu_i h(t),\ t \geq 0$$

where, as before, h is the failure rate of Y. Thus the proportionality assumption holds. Furthermore Y has IFR or DFR according as $\alpha \geq 1$ or $\alpha \leq 1$. For $\alpha = 1$, h is constant. A simple calculation will show $C_i(\infty) = \frac{1}{2}\mu_i(1 - \alpha^{-1})$ and so unless $\alpha = 1$, no two mortality rates will be asymptotically independent.

4. Proof of Proposition

From (6), (8) and (13) one obtains for each $1 \leq i \leq k$, $t \geq 0$

$$n^{\frac{1}{2}}(\Gamma_{n,i}(t) - \gamma_i(t)) = \{n^{-1}T_n(t)\}^{-1}\{n^{-\frac{1}{2}}\sum_{\ell=1}^{n} Z_{i\ell}\} \tag{17}$$

where $Z_{i\ell} = I[Y_\ell \leq t,\ J_\ell = i] - \gamma_i(t)\{Y_\ell \wedge t\}$. Now, for each i, $1 \leq i \leq k$, the $Z_{i\ell}$, $1 \leq \ell \leq n$ are independent and identically distributed (iid) random variables. Also $E(Z_{i\ell}) = 0$. We need to compute $\mathrm{Cov}(Z_{i\ell},Z_{j\ell})$. For simplicity in script write $\eta_{i\ell} = I[Y_\ell \leq t,\ J_\ell = i]$. Then

$$Z_{i\ell}Z_{ij} = \eta_{i\ell}\eta_{j\ell} - \gamma_i(t)\{Y_\ell \wedge t\}\eta_{j\ell} - \gamma_j(t)\{Y_\ell \wedge t\}\eta_{i\ell} + \gamma_i(t)\gamma_j(t)(Y_\ell \wedge t)^2. \tag{18}$$

But $\eta_{i\ell}\eta_{j\ell} = 0$, if $i \neq j$

$= \eta_{i\ell}$ if $i = j$. (19)

Also $E\{(Y_\ell \wedge t)\eta_{i\ell}\} = \int_0^t y\, Q_i'(y)dy$, $1 \leq i \leq k$. (20)

Hence from (18) through (20), if $i \neq j$,

$$\mathrm{Cov}(Z_{i\ell},Z_{j\ell}) = -\gamma_i(t)\{\int_0^t y\, Q_i'(y)dy\} - \gamma_j(t)\{\int_0^t y\, Q_j'(t)dy\}$$

$$+ 2\gamma_i(t)\gamma_j(t)\{\int_0^t y\, S(y)dy\} . \quad (21)$$

Recall again (13) and (15). Then after some routine manipulations (21) can be rewritten

$$\mathrm{Cov}(Z_{i\ell},Z_{j\ell}) = -\{Q_i(t)C_j(t) + Q_j(t)C_i(t)\} \quad (22)$$

for all $t \geq 0$ and $1 \leq i, j \leq k$, with $i \neq j$. But from (18) and (19)

$$\mathrm{Cov}(Z_{i\ell},Z_{i\ell}) = \mathrm{Var}(Z_{i\ell}) = E\{\eta_{i\ell} - 2\gamma_i(t)(Y_\ell \wedge t)\eta_{i\ell} + \gamma_i^2(t)(Y_\ell \wedge t)^2\}$$

$$= Q_i(t) - 2\gamma_i(t)\int_0^t y\, Q_i'(y)dy + 2\gamma_i^2(t)\int_0^t y\, S(y)dy$$

$$= Q_i(t)(1 - 2C_i(t)),\ 1 \leq i \leq k,\ t \geq 0 . \quad (23)$$

To establish the proposition consider the random variable

$$X_n(t) = \sum_{i=1}^k a_i\{n^{\frac{1}{2}}(\Gamma_{n,i}(t) - \gamma_i(t))\} = \{n^{-1}T_n(t)\}^{-1}n^{-\frac{1}{2}}\sum_{\ell=1}^n Z_\ell^* \quad (24)$$

where the a_i's are arbitrary constants and the sequence $\{Z_\ell^*: 1 \leq \ell \leq n\}$ is given by

$$Z_\ell^* = \sum_{i=1}^k a_i Z_{i\ell} .$$

Hence by the Central Limit Theorem $n^{-\frac{1}{2}}\sum_{\ell=1}^n Z_\ell^* \to_D N(0,\sigma^2)$ with

$\sigma^2 = \sum_{i=1}^{k}\sum_{j=1}^{k} a_i a_j \operatorname{Cov}(Z_{i\ell}, Z_{j\ell})$. Also by the Strong Law of Large Numbers, $n^{-1}T_n(t) \to_{a.s.} \int_0^t S(y)dy$. Thus (24) leads to the convergence

$$X_n(t) \to_{\mathcal{D}} N(0, (\int_0^t S(y)dy)^{-2}\sigma^2). \tag{25}$$

Writing $\underset{\sim}{a} = (a_1, \ldots, a_k)$ and recalling (14) we have shown in (25) that $\underset{\sim}{a}\{n^{\frac{1}{2}}(\underset{\sim}{\Gamma}_n(t) - \underset{\sim}{\chi}(t))\}\underset{\sim}{a}^T \to N(0, \underset{\sim}{a}\,\underset{\sim}{\Sigma}\,\underset{\sim}{a}^T)$. So since $\underset{\sim}{a}$ is an arbitrary vector, the proposition is proven. The Corollary can be established along exactly the same lines.

5. Concluding Remarks

In this paper we have dealt with mortality rates evaluated in a life test or clinical trial under a basic competing risks model. The asymptotic multivariate normal distribution that we have obtained for the vector of these mortality rates also provides for inference on the parameters of our model. For instance confidence sets for the $\underset{\sim}{\chi}(t)$ can be supplied and tests of hypotheses on $\underset{\sim}{\chi}(t)$ obtained. We may also consider the stochastic process $t \to n^{\frac{1}{2}}(\underset{\sim}{\Gamma}_n(t) - \underset{\sim}{\chi}(t))$, $t \geq 0$ as an element in the function space $D^k[0,\infty)$ (the k-fold cartesian product of $D[0,\infty)$ space of right continuous real functions on $[0,\infty)$ with left hand limits) equipped with a suitable topology, and thus an invariance principle derived paralleling our Proposition. Furthermore appropriate stopping mechanisms defined in terms of $\underset{\sim}{\Gamma}_n(t)$ can be considered as for example the rule $\tau_n = \inf\{t > 0: \min_{1 \leq i \leq n} \Gamma_{n,i}(t) > a_n\}$, where the a_n are some constants.

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For a sample of individuals from an animal or human population under observation in a clinical trial or life test, mortality rates are defined for each risk to which the population is exposed. By considering only the crude risk functions and cause-specific failure rates in a basic competing risks model, these mortality rates are shown to have an asymptotic normal distribution. An expression for the asymptotic correlation between a pair of mortality rates is thus obtained and a necessary and sufficient condition for

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